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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,862	10/30/2003	Jingrong Cao	VPI/02-115 US	8080

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 07/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/696,862	CAO ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/21/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response, which included addition of new claims 54-56 and amendment to claims 1, 48, 50, 52 and 53, filed on 4/21/2006, is made of record. Claims 1-56 are now pending.

In view of applicants' response, the following rejections made in the previous office action are maintained.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed 4/21/2006, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following apply. Any claim not specifically rejected is rejected as it is dependent claim on a rejected claim and shares the same indefiniteness.

1. In claim 1, recitation of U and V as -PO- and -POR- renders claim 1 and its dependent claims indefinite, as it is not clear what else is appended to P to meet its valence requirement.

This rejection is same as made in the previous office action except that the newly added claims 54-56 are now included in this rejection. Applicants' amendment to the claim 1

did not obviate this rejection. The first choice –P(O)- still leaves P with tetravalent as O is doubly bonded to P. In addition a clarification is needed for $-P(O)_2-$ as P appears to be hexavalent in this case.

Hence, this rejection is proper and is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of obesity embraced, does not reasonably provide enablement for treating or lessening the severity of any or all diseases and disorder embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims 47-53 are drawn to method of inhibiting various kinases as well as treating various diseases and disorders and claim 46 drawn to a composition with intended use for treating various diseases.

Claims 47-53 are reach through claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions for which they lack written description and enabling disclosure in the specification.

In the instant case, because of the interaction of the compound formula I with various kinases, it is recited that instant compounds are useful for treating or lessening

the severity of any or all disorders and diseases selected from a prolferative disorder, a cardiac disorder, a neurogenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, viral disease, or a bone disorder for which there is no adequate written description and enabling disclosure in the instant specification. The scope of the claims includes any or all disorders/ diseases due to kinase activity (such as Rock, ERK2, GSK, AGC etc.) inhibition including those yet to be discovered as due said mode of action for which there is no enabling disclosure. In addition, the scope of these claims includes treating or lessening severity of various disorders and diseases that include a proliferative disorder, a cardiac disorder, an inflammatory disorder, an autoimmune disorder, a viral disease, or a bone disorder each of which would include any number diseases or disorders. For example proliferative disorders can include any cancer such as lung cancer, bone cancer, pancreatic cancer, skin cancer. cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region. stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal

pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. List of the other disorders would of course add to this hugh list of diseases, as well as those specifically claimed such as allergy, asthma, diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, Ams-associated dementia, amyotrophic lateral sclerosis (AML, Lou Gehrig's disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia, stroke, or baldness, various other neurodegenerative or neurological disorder, which are not adequately enabled solely based on the activity of the compounds provided in the specification. The instant compounds are disclosed to have kinase inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as kinase inhibitor shown in examples of pages 151-153, that would be useful for all sorts of disorders and diseases. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of neurological diseases, autoimmune diseases, proliferative diseases are very difficult to treat and despite the fact that there are many drugs with the same mode of action..

The scope of the claims involves thousands of compounds of claim 1 as well as the thousand of diseases embraced by the term disorder and disease

No compound has ever been found to treat all types of medical conditions generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of modern medicine. Proliferative disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper proliferation of the gastric epithelium caused by the Helicobacter pylori infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

No compound has ever been found to treat proliferative diseases of all types generally. The same is true for cardiac disorder, a neurogenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, viral disease, or a bone disorder. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Thus, it is beyond the skill of clinician today to get an agent to be effective against cancers

generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Kim et al., Current Opinion in Genetics and Development, 10, 508-514, 2000, Mass, R. D., Int. J. Radiation Oncology Bio. Phys.Vol. 58(3): 932-940, 2004 and Fabbro et al. Pharmacology & therapeutics 93, 79-98, 2002.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating disorders/diseases that require receptor kinase inhibitory activity.

2) The state of the prior art: Recent publications expressed that the receptor tyrosine kinase inhibition effects are unpredictable and are still exploratory. See Mass et al. and Fabbro et al., cited above especially the concluding paragraph.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating or lessening the severity of any or all disorders and diseases selected from a prolferative disorder, a cardiac disorder, a neurogenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, viral disease, or a bone disorder embraced for the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all disorders diseases such as treating or lessening the severity of any or all disorders and diseases selected from a prolferative disorder, a cardiac disorder, a neurogenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, viral disease, or a bone disorder and the state of the art is that the effects of kinase inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace treating or lessening the severity of any or all disorders and diseases selected from a prolferative disorder, a cardiac disorder, a neurogenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, viral disease, or a bone disorder including those yet to be related to kinase.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion

is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive.

First of all, as noted above, instant claims 48 and 49 are reach through claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions for which they lack written description and enabling disclosure in the specification.

In the instant case, because of the interaction of the compound formula I with various kinases, it is recited that instant compounds are useful for treating or lessening the severity of any or all disorders and diseases selected from a prolferative disorder, a cardiac disorder, a neurogenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, viral disease, or a bone disorder for which there is no adequate written description and enabling disclosure in the instant specification.

As can be seen from the definition of the term "biological sample" stated in page 109 of specifcation, without limitation it reads on many and all types of biological samples, which can include mammals or animals and therefore, the claimed method is seen to encompass an inhibitory method wherein the compound is administered to an animal. This is further evident from the purpose of the inhibition of various kinases activity stated in specification at various places for treating various diseases. As the

inhibition of kinases in a biological sample is disclosed to be useful, it implicitly reads on the inherent therapeutic methods characterized by the activity, which as per the specification includes numerous types of diseases/disorders recited in specification.

The sole testing assay provided in the specification at pages 151-152 is to test the ability of the compounds to inhibit ROCK, ERK, PKA or GSK activity using a standard enzyme system, however, applicants have not provided how this correlates with the efficacy in all types of biological samples encompassed by the instant method and their use in the various purposes wherein the inhibition activity is useful. For example, blood transfusion is the process of transferring blood or blood-based products from one person into the circulatory system of another. Blood transfusions may be seen as a procedure to treat some medical conditions, such as massive blood loss due to trauma, surgery, shock and where the red cell producing mechanism (or some other normal and essential component) fails. Similarly, an organ transplantation is the transplantation of a whole or partial organ from one body to another (or from a donor site on the patient's own body), for the purpose of replacing the recipient's damaged or failing organ with a working one from the donor site. As can be seen from the above, without limitation these purposes are intended for therapeutic methods and applicant has not provided competent evidence sufficient to enable the claimed method.

Therefore, the instant claim appears to be directed to the various types of therapeutic methods.

Secondly, the references provided in the IDS still do not support treatment all diseases including various cancers. They do provide support for some specific diseases

and limiting to such diseases will no be objected if proper nexus is shown in the references. For examples some of the references stated in page 73 of the response relates treating specific cancers not all cancers. The list of cancers included in the claims 50 and 52 clearly lack support.

Similarly, applicants argued that because Hiroka et al. teaches hypotensive effect of ROCK inhibitors, there is support for treating any or all cardiovascular diseases. This not deemed as proper nexus for treating hypertension and any or all cardiovascular diseases.

Hence, this rejection is proper and is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-47 and 50-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Santora et al., WO 02/14311 for reasons of record. To repeat:

Santora et al. teaches several aminosubstituted heterocyclic compounds for treating stroke, which includes instant pyridylsubstittuted thiazole compounds. See page 6, formula 1 and note the definition of various variable groups. Especially note when R^2 is pyridiyl, ring A is thiazole ring as permitted in pages 6-16, with the given definition of Y, X, Z, compounds taught by Santora et al. include instant compounds. Note in page 12 various choices of Y are taught. More specifically see pages 16-17 formula II, pages 24-40, formula IV and Formula V, each of which clearly depicts instant pyridyl-thiazole compounds. See pages 40-56 for various species of compounds. See pages 155-285 for examples 1-233.

Instant claims exclude the compounds taught in thee examples by a proviso, particularly urea compounds i.e. Y in Santora et al is NHCONH group.

However, Santora et al. teaches several variations in Y as well as substituents on the pyridiyl-thiazole core. Although, Santora et al. does not exemplify all such

compounds, Santora et al., clearly teaches equivalency of those compounds taught in examples 1-233 with those generically recited in pages 6-40.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Santora et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

Applicants amendment to exclude from Q^1 the choice of CONR and from Q^2 the choice of NR', did not obviate this rejection.

First of all, the first choice of Y meets instant R^2-N-Q^1- requirement. This choice is clearly a preferred choice and more preferred choice along with the urea choice. The fact that urea is the most preferred choice does not negate the above said first choice as not relevant teaching.

Secondly, contrary to applicants urging, Santora et al. teaches equivalency of these choices and the embodiments with those compounds exemplified. It should be noted that applicants have also only exemplified some of R^2-N-Q^1-R^3 choices not all that is claimed. As much as applicants believe their genus is enabled for all compounds energetically embraced in formula, it is held that the genus of Santora on the same basis is equally enabled for all compounds of the genus of formula I. Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Santora et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

Hence, this rejection is proper and is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published

applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

7/9/2006